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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/738,413	12/17/2003	Ralph R. Binetti	SC66U-US	8915

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/738,413	BINETTI ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *31-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of group I, claims 1-15, and SEQ ID NO: 1, in the reply filed on 8/22/2005 is acknowledged. The examiner inadvertently omitted claims 16-30 from the restriction requirement. These claims will be examined with group I. Applicant points out that claims 16-38 were not a part of the restriction requirement. On the contrary, claims 31-38 were included in group II of the restriction requirement mailed on 7/20/05. Additionally, applicant response included an election of the "species" of SEQ ID NO: 1. It is noted that the restriction was not based upon a species election, but rather an improper Markush. Therefore, this is a group restriction rather than a species election.

Upon further consideration, claims 31-38 will be examined with the claims of group I. Therefore, claims 1-38 will be examined together.

Claims 39-41, and the subject matter not drawn to SEQ ID NO: 1, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claim Objections

Claim 4 is objected to because of the following informalities: SEQ ID NOs: 1 and 2 are each listed twice in the list of sequences. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of the above claims is drawn to a method comprising topically administering to the skin of a subject in need of treatment a composition comprising one or more siRNA specific for tyrosinase mRNA.

At the outset, it is noted that the claim does not recite a specific target nucleotide sequence by SEQ ID NO, but rather refer to the broad genus of tyrosinase sequences.

The claims encompass a method comprising topically administering to the skin of a subject in need of treatment a composition comprising one or more siRNA specific for tyrosinase mRNA, as well as encompass targeting any tyrosinase homolog or allele from any species known or yet to be discovered of tyrosinase, as well as DNA genomic fragments, spliced variants or fragment that retains tyrosinase-like activity. Although the specification discloses siRNA sequences having complementarity to a tyrosinase sequence, the specification does not describe siRNA molecules directed to any other species of tyrosinase to describe the instantly claimed genus of any tyrosinase mRNA. As evidenced by the prior art, tyrosinase is a large genus encompassing many different genes. For example, Ben-David et al. (US 6,573,050 B1) teach tyrosinase, TYRP1, and

TYRP2, each of which are encompassed in the instantly recited term "tyrosinase". Boonanuntanasarn et al. teach targeting siRNA molecules to the tyrosinase A gene. Each of these target sequences are different and one sequence is not predictive of another. One of ordinary skill in the art could not make such oligos to any tyrosinase mRNA without knowledge of the sequence since a representative sample of the instantly claimed genus of any tyrosinase mRNA sequence has not been adequately described. Given the breadth of sequences embraced in the instantly claimed genus, one could not envision the member oligonucleotides that target such a broad genus or recognize that the applicant was in possession of the claimed genus at the time of filing.

Claims 1-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Although the specification teaches a northern dot blot experiment to measure tyrosinase mRNA seen in B16 mouse melanoma cell line after 48 hour treatment with a tyrosinase siRNA *in vitro* (see page 17), the instant claims are drawn to methods in a subject in need of treatment. While this data might be suggestive of treatment, a mere suggestion does not overcome the unpredictability in the art of treatment in prevention. Furthermore, a connection between the instantly recited disorders and tyrosinase expression has not been firmly established. The instant specification is silent as to any

actual teachings of such treatment or prevention effects *in vivo*. The instant specification is not enabled for *in vivo* effects.

The instant invention is drawn to a method for treating hyperpigmentation, or other unwanted skin condition, or other unwanted pigmentation, comprising topically administering to the skin of a subject in need of treatment a composition comprising one or more siRNA specific for tyrosinase mRNA. The invention is further drawn to a method of improving the aesthetic appearance of the skin comprising topically administering a composition comprising one or more siRNA oligomers specific for tyrosinase. The instant claims are drawn to *in vivo* effects.

As explained in the written description rejection above, applicant is not claiming a specific target by SEQ ID NO, but rather is claiming a method comprising topically administering to the skin of a subject in need of treatment a composition comprising one or more siRNA oligomers specific for any tyrosinase mRNA. The broad genus of any tyrosinase target encompasses members of a vast family, wherein not all of the members of this family have shown to be associated with hyperpigmentation or other unwanted skin conditions. Applicant has not demonstrated that targeting such family members would result in the desired treatment effects in a subject in need of treatment. Additionally, the claims are specifically drawn to topical administration, although applicant, nor the relevant art, have not disclosed *in vivo* topical administration that has successfully treated the recited disorders.

The unpredictability of attenuating/inhibiting expression of a target gene in by RNA interference (RNAi) is evident in the art. While it is recognized that introduction of

dsRNA targeted to a specific gene may result in attenuation of expression of the targeted gene via RNAi, the degree of attenuation and the length of time that attenuation is achieved is not predictable. Caplen et al. (Gene 2000, vol. 252, p.95-105) provides evidence of the unpredictability of dsRNA attenuation/inhibition of a targeted gene in vertebrate cells *in vitro*. Caplen et al. report that although dsRNA inhibits gene expression in cultured *Drosophila* cells, screening of three commonly used cell lines from three different species: human, hamster, and mouse, using cells expressing transgenes both transiently and permanently, produced mixed results. Transient transfection of dsRNA targeted to the βgal transgene into 293 and BHK31 cells resulted either in no effect (293 cells) or a non-specific decrease in gene expression (BHK21 cells). Transfection of dsRNA into mouse NIH/3T3 cells transduced with a retrovirus expressing βgal induced no detectable decrease in gene expression (see pages 102-103).

The post-filing art of Zhang et al. (Current Pharmaceutical Biotechnology 2004, vol. 5, p.1-7) reviews the state of the art with regard to RNAi and has this to say about use in mammalian cells. "Use of siRNA in mammalian cells could be just as far-reaching, with the applications extending to functional genomics and therapeutics. But various technical issues must be addressed, especially for large-scale applications. For instance, dsRNA can be delivered to *C. elegans* by feeding or soaking, but effective delivery of siRNAs to mammalian cells will not be so simple."

Not only does the prior art demonstrate unpredictability of attenuating/inhibiting expression of a target gene in by RNA interference (RNAi), but the prior art also

evidences the unpredictability of treatment of skin disorders. The post-filing art teaching of Hartmann et al. discloses that therapeutic approaches are hampered by the fact that the pathophysiology of hypopigmentary disorders is still poorly understood.

In order to practice the claimed invention *in vivo* a number of variables would have to be optimized, including 1). determining what sequences would constitute antisense sequences against the DNA sequences encoding a target gene and what antisense sequences would actually be effective at inhibiting expression of the target gene, 2). the form of the oligonucleotide, whether to use a modified oligonucleotide with one or more backbone, sugar or base modifications, 3). the mode of delivery of the oligonucleotide to an organism that would allow it to reach the targeted cell, 4). the amount of oligonucleotide that would need to be delivered in order to allow inhibition of the expression of a target gene once it reached the proper cell and 5). ensuring the oligonucleotide remains viable in a cell for a period of time that allows inhibition of the gene to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each oligonucleotide duplex.

Thus, while the specification is enabling for the *in vitro* examples set forth in the specification, the specification is not enabling for introducing any dsRNA for tyrosinase mRNA in any cell or animal as the art of attenuating gene expression by introducing dsRNA into a cell or organism is neither routine nor predictable. Additionally, applicant is not only claiming treatment effects, but is also claiming prevention. Neither the instant specification nor the prior art exhibit prevention of any of the claimed disorders

via introduction of siRNA oligomers specific for tyrosinase. Applicant has not demonstrated that introduction of a siRNA oligomer specific for tyrosinase would prevent an unwanted skin condition or unwanted pigmentation. Thus, one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1-38 are not enabled.

Art of Interest

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Ben-David et al. (US 6,573,050 B1) is considered relevant but not applied as prior art as the instant claims are drawn to treatment in a subject in need.

Boonanuntanasarn et al. (Biochemical and Biophysical Research Communications, 310, 2003, pages 1089-1095) is considered relevant but not applied as prior art as the instant claims recite topical administration.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Amy H. Bowman
Examiner
Art Unit 1635

J.D. SCHULTZ, Ph.D.
PATENT EXAMINER